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09/679,331	10/04/2000	Pierre Deslongchamps	6670/0H748	6557

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EXAMINER
EPPERSON, JON D

ART UNIT	PAPER NUMBER
1627	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/679,331	Applicant(s) DESLONGCHAMPS ET AL.	
File Copy	Examiner Jon D Epperson	Art Unit 1627	

-- Th MAILING DATE of this communication appears on the cover sheet with th corr spond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *11-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Detailed Action

Status of the Application

1. Receipt is acknowledged of a response to a restriction requirement, which was dated on July 15, 2002 (Paper No. 7).

Priority Claims

2. The foreign priority filing date of September 4, 2002 was NOT granted because certified copies of the foreign priority documents were not received (See 35 U.S.C. § 119(a)-(d)).

Status of the Claims

3. Claims 1-23 are pending in the present application.

4. Applicant's election of Group I (claims 1-10) without traverse is acknowledged (see Paper No. 7). Claims 11-23 are cancelled without prejudice.

5. Applicant's election of species in Paper No. 7 with traverse is acknowledged (see below i.e., Response to Election of Species with Traverse).

6. Therefore, claims 1-10 are examined on the merits in this action. Please note that claims 1-3 are only examined to the extent of the elected species and/or subject matter (see MPEP § 803.02).

Response to Election of Species without Traverse

7. Applicant's election of species in Paper No. 7 with traverse is acknowledged. Applicant states that the election of a single species (as outlined in points 5 and 6) is "unnecessarily restrictive." Applicant further states that "[t]he use of generic formulas for closely related chemical species is a well-established practice in the art." Applicant further notes that other patents that describe routes to conformationally-restricted peptidometics allow similar claims to those in the current application and give US 5,618,914 as an example.

8. Applicant's arguments have been fully considered, but are not found persuasive. The examiner's position is that that species are distinct, each from the other, because the structures and modes of action of each of the species encompassed are different. They would also differ in their reactivity and/or mechanism and/or the products made. Therefore, the species have different issues regarding patentability and represent patentably distinct subject matter.

For example, applicant argues that "[t]he use of generic formulas for closely related chemical species is a well-established practice" and that "[t]he building blocks in claim 1 that comprise substructures A, B, and C of the claim are, for the most part, amino acids." The examiner contends that the generic formula used in claim 1 is broad and reads on an enormous number of patentably distinct compounds. The "building blocks" in claim 1 do not just read on

amino acids. The building blocks also read on beta amino acids, gamma amino acids, non-natural amino acids, D/L amino acids. Furthermore, the "building block" that comprises the substructure T reads on a great deal of unrelated compounds along with the N-substituted core structure. Therefore, the "use of generic formulas" in this case does not represent the "well-established practice" of denoting closely related chemical species because the structures represented by the formula in claim 1 are not "closely-related." Also note that applicant has already conceded that the breadth of the claims is broad (see specification, page 12, second paragraph) ("the scope of the invention is broad") and that these compounds would not be structurally related in form and function (see specification, page 12, second paragraph) ("the compounds ... can adopt structures very different from conventional β-turns, according to the nature of their spacer parts"). Finally, the argument that other patents have "allow[ed similar claims" is not material because each cased is examined on its own merits.

As also stated previously, the different species would require different searches and there is no expectation that the searches would be coextensive. The examiner maintains that this does create an undue search burden.

However, it was also stated that upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

Finally, it was also stated that should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record

showing the species to be obvious variants or clearly admit on the record that this is the case. This has not been done.

Thus the species election is deemed proper and is maintained.

9. As a result, the restriction requirement and/or election of species is still deemed proper and is therefore made FINAL.

Objections to the Claims

10. Claim 10 is objected to because of the following informalities:

Claim 10 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form or rewrite the claim(s) in independent form. Claim 10 depends from claim 1. Claim 1 recites a "macrocyclic compound of the formula (I)." Claim 10 recites compounds that do not fall within the definition of claim (I). For example, claim 1 requires a compound to have the formula $-C(=O)-CH(-R_1)-(CH_2)_x-N(-X)-(T)$, wherein T is Y-L-Z (note that L is $-(CH_2)_d-A-(CH_2)_j-B-(CH_2)_e-$ and Y is $-CH_2-$ or -CO- and Z is -NH- or -O-) and d and e being independently an integer from 1 to 5. However, the compounds in claim 10 do not have the same -(T)- moiety as the compounds in claim 1 because the value of d (in the L formula $-(CH_2)_d-A-(CH_2)_j-B-(CH_2)_e-$) for the compounds in claim 10 is zero i.e., does not fall within the range of 1 to 5. The $-NH_2-CH_2-CH=CH-$ part of the top left structure in claim 10, for example, has $Y = CH_2$ (note that parent structure $-C(=O)-CH(-R_1)-(CH_2)_x-N(-X)-(T)$, wherein T = Y-L-Z) and L = -CH=CH-

CH_2-, but does not have the required -$(CH_2)_d$- where d is from 1 to 5 (i.e., in this case d is zero, which does not fall within the scope of claim 1). Claim 10, therefore, does not further limit claim 1.

Claims Rejections - 35 U.S.C. 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

To satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. Applicant's claim is directed to a "macrocyclic compound of the formula (I)." There are virtually an unlimited number of compounds that would fall within the scope of this claim because applicant claims not only amino acids with various side chains, but also β-amino acids, γ-amino acids, non-natural amino acids, D and L amino acids and various other spacer groups that can all be varied independently of one another to form a macrocyclic compound. Furthermore, the enormous number of chemical species that would fall within this formula are not "closely related" because the

numerous substitutions that have been suggested would change the overall structure of the compounds in ways that would materially effect its form and function. For example, applicant concedes "the compounds according to the invention ...can adopt ***very different structures*** ... ***according to the nature of their spacer parts*** [and, as a result] the ***scope*** of the invention ***is broad***" (see specification page 12, paragraph 2). Furthermore, the connectivities for many of the variable substituents have not been specified (see 35 U.S.C. 112, second paragraph rejections below) and, consequently, it is not possible to determine what the full scope of the claimed invention is. As a result, applicants have not demonstrated in "full, clear, concise, and exact terms" that they are in possession of the elected invention.

With respect to adequate disclosure applicant is referred to the discussion in *University of California v. Eli Lilly and Co.* (U.S. Court of Appeals Federal Circuit (CAFC) 43 USPQ2d 1398 7/22/1997 Decided July 22, 1997; No. 96-1175) regarding disclosure. For adequate disclosure, like enablement, requires *representative examples* which provide reasonable assurance to one skilled in the art that the compounds falling within the scope both possess the alleged utility and additionally demonstrate that *applicant had possession of the full scope of the claimed invention.* See *In re Riat* (CCPA 1964) 327 F2d 685, 140 USPQ 471; *In re Barr* (CCPA 1971) 444 F 2d 349, 151 USPQ 724 (for enablement) and University *of California v. Eli Lilly and Co* cited above (for disclosure).

The few examples provided by applicant is neither representative of the claimed genus, nor does it represent a substantial portion of the claimed genus. Furthermore,

since it is not even possible to determine what the full scope of the claimed invention is (see 35 U.S.C. 112, second paragraph rejections below), applicant cannot be in possession of the full scope of the invention. Therefore, the subject matter was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the full scope of the claimed invention.

12. Claims 1-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a few of the compounds that fall within the broad scope of the claimed invention (see below), is not enabling for the vast majority of compounds that fall within this broad scope. This is an enablement rejection.

Any person skilled in the art to which it pertains, or with which it is most nearly connected, would not know how to make and use the claimed invention. Applicant has not provided enough examples of how to use the claimed invention to be enabling for the full breadth of the claims. It is clear from applicant's specification how one might practice this invention with the top two compounds in claim 10 because they mimic RGD and it is clear from the specification and known in the literature that these compounds might show similar biological activity to known RGD compounds (see specification, page 11, first paragraph, which teaches a known use in the literature for RGD compounds in cell recognition). However, applicant has not provided sufficient guidance as to how to make/use **any** of the other compounds that might fall within the broad scope of the claimed invention, which are not related to RGD compounds.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors include, but are not limited to:

(1) the breadth of the claims;
(2) the nature of the invention;
(3) the state of the prior art;
(4) the level of one of ordinary skill;
(5) the level of predictability in the art;
(6) the amount of direction provided by the inventor;
(7) the existence of working examples; and
(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

See *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(1-2) Breadth of the claims and nature of the invention: Applicant concedes that the breadth of the claims is broad (see specification, page 12, second paragraph) ("the scope of the invention is broad"). Applicant's formula (I) for a macrocyclic compound in claim 1 reads on an almost unlimited number of compounds because of the enormous number of variable groups that can be independently changed. For example, a variable number of amino acids, β-amino acids, γ-amino acids, non-natural amino acids, D and L amino acids and various spacer groups all containing various R side chains can be independently varied. Furthermore, applicant concedes that these compounds would not be structurally related in form and function (see specification, page 12, second paragraph) ("the compounds ... can adopt structures very different from conventional β-turns, according to the nature of their spacer parts"). In addition, it is not possible to determine what effect these substitutions and changes in conformation will have on the therapeutic value

(if any) of these macrocyclic compounds i.e., the nature of the subject matter is completely unpredictable (see Parsons et al, conclusion) ("The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a prior* but must be determined from case to case by painstaking experimental study").

(3 and 5) The state of the prior art and the level of predictability in the art: The therapeutic value for the vast majority of these macrocyclic compounds is not known in the literature. Furthermore, it would be hard to predict what biological target should be used to screen many of these compounds for biological activity and even harder to predict whether or not they would show biological activity (see Parsons et al, conclusion) ("The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a prior* but must be determined from case to case by painstaking experimental study"). Even if a biological target was known, the structures of the possible variants are sufficiently diverse that one of ordinary skill would not be able to predict which compounds would be capable of binding to the given biological target. Therefore, the state of the prior art and the level of predictability in the art is quite low.

(4) The level of one of ordinary skill: The level of skill would be high, most likely at the Ph.D. level. Such persons of ordinary skill in this art, given its unpredictability, would have to engage in undue (non-routine) experimentation to carry out the invention as claimed.

(6-7) The amount of direction provided by the inventor and the existence of working examples: Applicants have not provided any examples for the vast majority of

compounds that fall within the scope of these broad claims which show their usefulness. Therefore, one of skill in the art would not know how to use the claimed invention (with the exception of the RGD analogs as mentioned above). Furthermore, there is no generic strategy for determining what effect these substitutions and resulting conformational changes will have on the binding affinity and/or selectivity. In addition, there is no "core" structure from which a biological entity might bind to. The only constant "core" structure given by general formula (I) is an amide bond and, as a result, there can be no common structural motif to which a biological ligand of interest would bind.

(8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure: The instant specification for all the reasons asserted above does not provide to one skilled in the art a reasonable amount of guidance with respect to the direction in which the experimentation should proceed in making and using the full scope of the claimed compounds. For example, it is not clear what immediate value a compound of formula (I) would have to the public when the (A) part represents a γ-amino acid with a methyl side chain, the (B) part represents a β-amino acid with an aromatic ether side chain, (c) represents a D-amino acid with a methionine side chain, the tether portion is $-CH_2-S-CH_2-$ and the "constant region" is a glycine radical. It would take undue experimentation to determine this value because as applicant concedes the "compounds according to the invention have much flexibility and can adopt structures very different from conventional β-turns, according to the nature of their spacer parts." Furthermore, applicant concedes that the vast majority of these compounds are only "potentially" useful in a research setting (see specification, page 19, second paragraph)

("Among the potential uses of the compounds according the present invention are uses in scientific research as research reagents") and only provides a long "non-specific" list of potential diseases where these macrocyclic compounds "might" some day be useful (see pages 18-19 showing a long non-specific list of potential diseases). Note that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. *In re Vaeck*, 947 F.2d 488, 496 & n.23, 20 USPQ2d 1438, 1445 & n.23 (Fed. Cir. 1991). Therefore, it is deemed that further research of an unpredictable nature would be necessary to make or use the invention as claimed. Thus, due to the inadequacies of the instant disclosure, one of ordinary skill would not have a reasonable expectation of success and the practice of the full scope of the invention would require undue experimentation.

Claims Rejections - 35 U.S.C. 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 1-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. In claim 1, parts (A), (B) and (C) of formula (I) are vague and indefinite. It would appear that several of the bonds are missing in the first bivalent radical i.e., it should read

-C(=O)-CH(-R_2)-(CH_2)$_y$-NH- wherein the carbonyl double bond and the side chain single bond are clearly shown (these bonds are currently missing). Applicants are requested to clarify and/or correct. Therefore, claim 1 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

B. In claim 1, the side chains of the macrocylic ring represented by formula (I) are vague and indefinite because it is not clear what structures many of these side chains represent and it is also not clear how (at what position) many of the side chain groups are covalently attached to the macrocycle. For example, applicant shows R_0, R_1, R_2, R_3 and R_4 to be independently selected from a large group (bottom of page 46 and top of page 47) wherein one of the members can be a benzyl or possibly and ethyl benzene group (bottom of page 46, top row, second compound to the left). It is not clear whether the horizontal line in this structure indicates a point of attachment or a bond to a terminal carbon. Furthermore, it is not clear whether this side chain group can bind via the aromatic ring instead of the terminal aliphatic carbon? Applicants are requested to clarify and/or correct for all ambiguous side chains e.g., R_0, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, X, etc. Therefore, claim 1 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

C. In claim 1, the internal groups of the bivalent L, A and B are vague and indefinite because it is not clear what structures A and B represent and it is also not clear how (at what position) many of the A and B groups are covalently attached to the L bivalent radical. For example, applicant shows A and B to be independently selected from a large group (page 49) wherein one of the members can be an epoxide (see page 49, 1/3 down

the page). It is not clear whether the horizontal lines in this structure indicate points of attachment or bonds to terminal carbons. Furthermore, it is not clear whether this side chain group can bind to the macrocycle via the tertiary carbon or whether it has to bind via the primary carbon? Applicants are requested to clarify and/or correct for all ambiguous groups. Therefore, claim 1 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

D. Claim 1-10 recite (on multiple occasions) improper Markush format. For example, claim 1 reads in part on page 48, "R8 ... selected from the group consisting of ... Cl, Br, I;" The claim should reads "R8 ... selected from the group consisting of ... Cl, Br, and I" Examiner suggests that applicant use the standard Markush language; see MPEP 2173.05(h) concerning ***all*** of the alternative expressions in claim 1:

> Alternative expressions are permitted if they present no uncertainty or ambiguity with respect to the question of scope or clarity of the claims. One acceptable form of alternative expression, which is commonly referred to as a Markush group, recites members as being "selected from the group consisting of A, B and C." See Ex parte Markush, 1925 C.D. 126 (Comm'r Pat. 1925).
>
> When materials recited in a claim are so related as to constitute a proper Markush group, they may be recited in the conventional manner, or alternatively. For example, if "wherein R is a material selected from the group consisting of A, B, C and D" is a proper limitation, then "wherein R is A, B, C or D" shall also be considered proper.

D. In claims 2, 4, 5 and 7, the phrase "commonly used for orthogonal protections" is vague and indefinite? Who is it "commonly used" by? What if other protection groups are "commonly used" ten years from now? Will the scope of the patent change? Applicants are requested to clarify. Therefore, claims 2, 4, 5 and 7 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

Status of Claims/Conclusion

14. No claims are allowed. However, claim 10 would be allowable if all other compounds were deleted from claim 10 other than the top two "RGD" mimics and if rewritten to overcome the rejection(s) under 35 U.S.C. 112, 2nd paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (703) 308-2423. The examiner can normally be reached Monday-Friday from 8:30 to 4:30.

16. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on (703) 308-4537. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

17. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-2439.

BENNETT CELSA
PRIMARY EXAMINER

Jon D. Epperson, Ph.D.
September 5, 2002